REMARKS

The Office Action mailed November 10, 2009 presents the examination of claims 1-4, 7-9 and 11-15. The present paper amends claims 1, 4, 14 and 15 and adds new claims 16-18 for consideration.

The amendment to claim 4 corrects a grammatical error.

The amendment to claim 14 recites a selection among alternatives recited in claim 1.

Support for the amendment to claim 1 is provided at least by the Examples of the specification, which show instances of measurement of either the total amount of 25-hydroxy vitamin D and 1α,25-dihydroxy vitamin D in a sample (e.g. Example 3) and measurement of 1α,25-dihydroxy vitamin D particularly following its separation from a serum sample. Thus, the term "and/or" is appropriate in claim 1.

The amendment to claim 15 is supported at least by Example 9 of the specification.

New claims 16-18 are supported by the specification at least by Example 9.

Rejection under 35 USC § 112, second paragraph

Claims 1-4, 7-9 and 11-15 are rejected under 35 USC § 112, second paragraph as allegedly being indefinite for failure to recite the particular steps of a "competitive binding assay." This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

With respect to claims 4 and 7-9, the Examiner is reminded that these claims are directed to kits, and thus it would be inappropriate to require recitation of detailed "active method steps".

With respect to claims 1-3 and 11-15, Applicants submit that the "invention" in the present instance is not in the use of a competitive assay particularly, but rather in the use of the particular ligand of formula (I). Thus, claim 1 clearly describes that the ligand is used at the step of displacing 25-hydroxy vitamin D or 1α,25-dihydroxy vitamin D from a vitamin D binding protein during such a competitive binding assay. Applicants submit that one of ordinary skill in

the art is well-versed in competitive binding assays, and in view of the nature of the invention, it is not necessary to recite each step in the assay process.

In this regard, Applicants point out that the IUPAC Compendium of Chemical Terminology, 2nd Ed., (1994) at page 2516, defines a "competitive binding assay" as, "An assay based on the competition between a labeleled and an unlabelled ligand in the reaction with a receptor binding agent (e.g. antibody, receptor, transport protein)."

Applicants also provide Exhibits 1-4, Taylor et al., Hawa et al., Armbruster et al. and Erlichman et al., respectively, describe competitive binding assays for a number of different analytes and using various different formats. The Examiner might also refer to the ALPCO product manual previously made of record as a further example. Indeed, the literature describing various competitive binding assays for different analytes is very, very great in extent.

The manner and details of conducting competitive binding assays are well-known to one of ordinary skill in the art of immunoassay. The essential step of all such assays of " comprising measuring displacement of..." is recited in claims 1-3 and 11-15, and therefore the claims are not indefinite and the instant rejection should be withdrawn.

The Examiner further criticizes claim 14 as being unclear as to how it can be the case that 25-hydroxy vitamin D is measured if it has been removed from the sample. The Examiner should consider that, if 25-hydroxy vitamin D is removed from the sample, then the assay will measure the amount of 1,25-dihydroxy vitamin D remaining in the sample. That is, the amount of 25-hydroxy vitamin D will be zero. Applicants note Example 9 presented at page 33 of the specification, providing an example of an assay conducted in such a fashion.

Claim 1 is amended to recite alternatives of measuring either 25-hydroxy vitamin D and 1α,25-dihydroxy vitamin D or only 1α,25-dihydroxy vitamin D, and claim 14 is amended to clarify that the latter alternative is selected, thus obviating this basis for rejection. Should the Examiner object to the "and/or" terminology, he is respectfully requested to suggest alternative language that he finds appropriate.

The Examiner further criticizes claim 15 as setting forth a use of the antibody, but not including any steps for that use. Claim 15 is amended to recite a particular application of the antibody, thus obviating this reason for rejection.

Rejection under 35 USC § 101

Claim 15 is rejected under 35 USC § 101 as failing to recite any particular process steps. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that claim 1, from which claim 15 depends, recites process steps. Further, claim 15 is amended to clarify the purpose of use of the antibody and so this ground of rejection is addressed and the instant rejection should be withdrawn.

Rejection under 35 USC § 112, first paragraph

Claims 1-3 and 11-13 are rejected under 35 USC § 112, first paragraph, for alleged lack of enablement of measurement of the amount of 1α,25-dihydroxy vitamin D in the presence of 25-hydroxy vitamin D. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that this rejection is wholly without basis. Although it may be the case that quantitation of 1α,25-dihydroxy vitamin D in a sample of human serum would benefit from separation of that compound from 25-hydroxy vitamin D, the present claim 1 recites the essential step of such an assay. The question of enablement relates to what the specification teaches one of ordinary skill in the art, and such separation is described in the specification for the instance of assay of 1α,25-dihydroxy vitamin D. The Examiner should note, e.g. the working example 9 beginning on page 33, line 18, and also as previously pointed out, at page 17, lines 26 ff. Applicants note the prior art includes an antibody specific to 1α,25-dihydroxy vitamin D as noted in Example 9. The Examiner might also consider that such antibody specific for binding 1α,25-dihydroxy vitamin D can be used as the "vitamin D binding protein" from which the ligand is displaced, as recited in the present claim 15 and as described in Example 9 at p. 33, lines 20-32.

As the specification fully enables the invention, the instant rejection should be withdrawn.

Rejection over prior art

Claims 1-4, 7-8 and 11 are rejected under 35 USC § 103(a) as being unpatentable over Holick WO '127. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants have repeatedly argued that the "displacement ligand" of Holick WO '127 is different from the present ligand of formula (I) and that it shows a different experimental result with respect to displacement efficiency. Applicants thus reiterate their prior argument here for the convenient review by the Examiner:

> Claims 1-4, 7-8 and 11 are rejected under 35 USC § 103(a) as being unpatentable over Holick et al. WO '127. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested. Claim 9 is rejected under 35 USC § 103(a) as being unpatentable over Holick et al. WO '127 in view of DeLuca '770. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.
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> As Applicants have previously argued, the Examiner fails to establish *prima facie* obviousness of the invention. The compounds synthesized by Holick '127 as the displacement ligand (corresponding to the "vitamin D derivative of formula (I)" in the present claims) are distinct from the vitamin D derivative of formula (I) of the instant invention. Furthermore, Holick's displacement ligands demonstrate a displacement efficiency approximately 1/11 that of the present compounds of formula (I) now claimed.
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> The Examiner has tried to explain that Holick WO '127 does actually make the displacement ligand of the present invention or one very similar to it. But, the Examiner has never explained how, if the compound of Holick WO '127 is so similar to that of the present invention, so much lower a displacement efficiency is seen. Instead, the Examiner simply dismisses the experimental results presented in Holick WO '127 and asserts that similar compounds are expected to show similar experimental effects.
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> Applicants submit that it is improper for the Examiner to ignore this discrepancy in his reasoning. That is, if indeed Holick's compounds are similar to those of formula (I) in the present claims, then they should show the same displacement efficiency, not displacement efficiency 1/11 that observed for the compounds of formula (I).
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> Applicants insist that if the Examiner is going to maintain the instant rejection that he resolve the discrepancies noted above and provide evidence to support his reasoning.

Furthermore, Applicants point out that the examples described by Holick in US 6,291,693 B1 (examples 8 and 9) do not work and cannot work. When the displacement efficiency of the tracer is less than 0.1 (1110'h) on DBP (the the naturally occurring vitamin D binding protein) then it should be clear to a skilled person that the biotin tracer cannot distinguish between 25-hydroxy vitamin D and 1 a,25-dihydroxy vitamin D, notably, when they are present in human serum in a ratio of 1000:1.

Thus, in example 9 of the instant application the method of measurement comprises a step of purifying and isolating la,25-dihydroxy vitamin D on a column and using an antibody specific for la,25-dihydroxy vitamin D to obtain the necessary specificity. In other words, the measurement is preceded by an isolation step combined with the use of an anti-1 a,25-dihydroxy vitamin D antibody as binding protein and the use of a tracer which has a displacement efficiency of 1 to achieve the required overall specificity.

The instant rejection should be withdrawn.

Obviousness-type double patenting

Claims 1-4, 7, 8 and 11-13 are rejected under the doctrine of obviousness-type double patenting over claims 1-5 of US 6787660. A Terminal Disclaimer will be filed upon a finding of otherwise allowable subject matter in this application.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachments:

Exhibits 1 - 4